Support for the limitation "compressed" as it appears in the claims may be found in the specification at page 9, lines 2-9 and page10, lines 1-2.

Support for the amendment "at least one" pharmaceutically acceptable "additive" as it appears in the claims may be found on page 6, line 9 and page 5, line 18.

Support for the amendment "containing more than 35% by weight of valsartan or a pharmaceutically acceptable salt thereof" in claim 18 may be found on page 2, lines 2-13.

Support for the amendment made to claim 18, step (i) may be found on page 8, line 30, page 9, line 1 and lines 14-30 and page 14, lines 12-13.

Support for the amendment made to claim 22 may be found on page 11, lines 2-4.

Support for the new claims may be found in the application and claims as originally filed as provided in detail below:

Claim---Support

29--- page 7, lines 1-4 and page 12, lines 1-7

30--- page 7, lines 25-30

31--- page 2, lines 2-13; page 1, lines 1-3 and 25-28; page 6, line 9; page 5, line 18, page 8, lines 27-30 and page 9, lines 1-7.

32--- page 10, lines 1-3

33--- page11, lines 10-13

34--- page 11, lines 14-28

35--- page 10, line 8; page 11, lines 2-4

36-- page 10, lines 1-3

37--- page 11, line 9

38--- page 14, example 1

39--- page 8, lines 4-11

40, 45---page 12, lines 12-17

41, 46---page 12, lines 18-21

42,47---page12, lines 24-27

43, 48---page12, lines 28-30; page 13, line 1

44, 49---page13, line 1

50, 51---page 8, line 30; page 9, lines 14-30; page 14, example 1

52, 53---page 9, line 9

54, 55---page 8, lines 5-12.

Claim 28 was rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, the amendment adding claim 28, in which a method of treating headache or chronic heart failure is claimed, represents a departure from the specification and the claims as originally filed by Applicant and the Applicant has not pointed out where the support comes from. In response, Applicants respectfully submit that support for claim 28 may be found in claim 27 as originally filed as well as on page 5, last paragraph of the priority document, GB 96113470, a copy of which is provided for the Examiner's convenience. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner rejected Claims 1-3 under 35 U.S.C.103(a) as allegedly *prima facie* obvious over Muller et al. (Eur. J. Clin. Pharmacol. 47:231-245 (1994), hereafter "Muller") in view of Makino et al. (U.S. Patent 5,501,861, hereafter "Makino"). According to the Examiner, Muller discloses use of valsartan as an antihypertensive drug, while Makino discloses a method of producing a fast

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dissolving tablet by compression molding a pharmacologically active ingredient which may be an antihypertensive drug, and which may contain additives. The Examiner also contends that Makino teaches that the recommendable proportion of the active ingredient in the composition is generally about 0.05 to 90% by weight, preferably 0.1 to 70% and more preferably 0.3 to 60% by weight. The Examiner then concludes that it would have been obvious to one of ordinary skill in the art to synthesize a solid oral dosage pharmaceutical composition of valsartan using the compression molding techniques of Makino. The Examiner is also of the opinion that one of ordinary skill in the art would have been motivated to synthesize the pharmaceutical composition of valsartan and additives by compression methods to increase the proportion by weight of active ingredient and achieve a faster disintegration rate of the oral preparation. Applicants respectfully disagree.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.
>
> Section 706.02(j) M.P.E.P. (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

In this case, the combination of references cited by the Examiner provides no teaching, suggestion or motivation to produce the solid dosage forms of valsartan as claimed by Applicant. Muller teaches a valsartan capsule and does not teach whether the capsule is a compressed dosage form. Muller also fails to disclose any detail about the formulation of the valsartan capsule. Indeed, Muller lacks any disclosure regarding the relative weight of valsartan in the capsule.

"A single line in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness." *Bausch and Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.* 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). In this case, Applicants respectfully submit that

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the Examiner's reliance on two incidental sentences in Makino and a hindsight reconstruction of Applicants' invention fails to set forth a proper *prima facie* rejection. Makino's bare mention of "antihypertensives" as one of at least 25 broad classes of therapeutic indications for active ingredients provides, at best, a tenuous link to the Muller disclosure. In addition, Makino's generic statement that the "active ingredient" can be present in an amount ranging from 0.05 to 90% would not have reasonably caused the skilled artisan to refer back to Makino's fleeting mention of "antihypertensives" *and then* combine these two broad disclosures with the teaching of a valsartan capsule by Muller.

Additionally, the emphasis in Makino is on the production of porous tablets for fast buccal dissolution. Applicants respectfully submit that Makino's disclosure of compression molding a porous buccal tablet provides absolutely no guidance for making the compressed dosage form of valsartan disclosed by Applicants. Indeed, one of skill in the art understands that buccal administration of a drug is indicated for highly potent drugs where small amounts are clinically effective. In this case, the high dose of valsartan disclosed in the instant invention would not be suitable for buccal administration. Additionally, one of skill in the art understands that the low tissue permeability and bitter taste of valsartan are additional reasons why buccal administration of this compound is contraindicated. Thus, Makino's focus on the production of porous tablets for fast buccal dissolution further weakens the alleged link between "antihypertensives" generally in Makino and valsartan in Muller. Without such teaching in the prior art, Makino's mere mention of "antihypertensives" and a wide, generic weight ratio of an active ingredient have virtually no relevance to either Muller or Applicants' claimed invention.

Moreover, Applicants respectfully submit that Makino's overly broad statements provide no reasonable expectation of success to the skilled artisan as the Examiner contends. Again, the Examiner melds Makino's separate statements regarding "antihypertensives" and the broad range

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of 0.05-90% to allege that one would have expected success in compressing a valsartan tablet containing more than 35% by weight valsartan. Makino's broad statements, however, fail to address any problems that would affect the expectation or predictability of success. For example, the bioavailability of such a valsartan tablet, the tablet strength and integrity before and after administration to the patient, safety, efficacy or ease of manufacture of the tablet on any significant scale are significant issues in this technology but are not discussed. In fact, valsartan has a very low density and is, therefore, rather bulky which makes it very difficult to formulate in a compact shape. As such, the manufacture of small, high dosage compressed tablets of valsartan is surprising, a fact which weakens the Examiner's contention that one skilled in the art would have reasonably expected that valsartan could be successfully made into a compressed dosage form containing at least 35% of the active ingredient.

Furthermore, the production of the tablets in Makino requires water. Indeed, "if the amount of water is too small, the mechanical (falling impact) strength of tablets will not be sufficiently high..." (Column 6, Lines 26-28). In stark contrast, contrary to conventional procedures, the production of the tablet core in the instant invention does not involve the use of water. Thus, Makino actually teaches away from Applicant's process and therefore the combination of Muller and Makino cannot render Applicant's invention prima facie obvious. Additionally, claims which recite that the coprimate is formed by compression in the absence of water have been included in the instant invention. Thus, since the cited references do not teach or suggest all the claim limitations of Applicants' invention, there is no *prima facie* case of obviousness. For this reason, as well as the arguments presented above, Applicants respectfully request that this rejection be withdrawn.

The Examiner also rejected Claims 4-17, 25 and 28 under 35 U.S.C. 103(a) over Muller, Makino and further in view of dePadova (U.S. Patent 5,464,854), Fujimura et al. (*Japanese Pharmacology and Therapeutics*, 23(12):3241-3247 (1995), hereafter "Fujimura"), Armah et al.

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(U.S. Patent 4,952,410, hereafter "Armah"), Ku et al. (U.S. Patent 5,994,348, hereafter "Ku") and Dopper et al. (U.S. Patent 5,527,543, hereafter "Dopper").

dePadova teaches the use of valsartan (0.5 mg-500 mg/day) in combination with hydrochlorothiazide (HCTZ) (6.25-12.5 mg/day) to treat premenstrual syndrome.

Fujimura discloses the use of valsartan (3mg/kg) in combination with HCTZ (5 mg/kg) to treat male spontaneously hypertensive rats.

Armah discloses pharmaceutical compositions of moxonidine and HCTZ for use as an antihypertensive, for example, tablets that contain 0.2 mg moxonidine and 12.5 mg HCTZ.

Ku teaches the formation of tablets containing irbesartan (preferably 75-300 mg) with or without HCTZ (6.25 to about 25 mg) to treat hypertension. Tablets are preferably prepared with a wet granulation process in which the total amount of water employed can be up to 50% of the total solids weight (Column 6, Lines 27-31; Column 7, Lines 64-67). The Examiner points out that microcrystalline cellulose in the range of 5-15% is disclosed as a diluent or disintegrant in this reference.

Dopper teaches a process to prepare granules of steroids. The granules can be used to make stable solid pharmaceutical units such as tablets. The Examiner points out that this reference discloses the use of cross-linked polyvinylpyrolidone (PVP) as a disintegrating agent.

The Examiner concludes that it would have been *prima facie* obvious to make a solid oral composition (tablet) of valsartan with or without HCTZ, given the compression method disclosed in Makino and in view of the dosages of antihypertensives, HCTZ and additives allegedly disclosed in the additional references. Applicants respectfully disagree.

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In response, Applicants respectfully reiterate the arguments made above regarding Muller and Makino and further submit that there is no suggestion or motivation in the dePadova, Fujimura, Armah, Ku, and Dopper references to modify the references or to combine the reference teachings to make Applicant's invention with a reasonable expectation of success. Thus, the cited references do not render Applicant's invention *prima facie* obvious. Applicants respectfully submit that it appears that the Examiner has relied upon hindsight reconstruction of Applicant's invention in citing these references to allege that the drug dosages, ratios and additives disclosed therein render Applicant's invention *prima facie* obvious. Applicants respectfully point out that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants respectfully submit that the Examiner has done exactly that in order to make this rejection and for this reason and the reasons discussed above, Applicants respectfully request that this rejection be withdrawn.

The Examiner also rejected Claims 18-24 under 35 U.S.C. 103(a) as allegedly unpatentable over Muller, Makino, dePadova, Fujimura, Armah, Ku, Dopper and further in view of Lachman et al. (The Theory and Practice of Industrial Pharmacy, Lea & Farbinger, eds., Philadelphia, pp. 318-320, hereafter "Lachman") and Tamas et al. (U.S. Patent 4,748,023, hereafter "Tamas").

Lachman briefly describes the method of compression granulation. The Examiner points out that this reference indicates that this process may involve slugging, followed by screening and that a roller compactor may be used.

Tamas discloses the preparation of sustained release tablets containing a composition of at least 80% active ingredient. The Examiner is of the belief that this reference teaches that powder

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mixtures can be pressed into tablets under a pressure of 100-120 kN. The Examiner may be mistakenly referring to the breaking strength of the tablet described in Example 1 (Column 6, Lines 27-28). In fact, according to the table provided with Example 2, a pressing strength of 10000 and 15000 kN appears to have been used to make the sustained release tablets disclosed therein (Column 7, Lines 55-68). (As these pressing strengths are rather remarkable, one of skill in the art might question whether these numbers are in error.)

The Examiner contends that it would have been obvious to one having ordinary skill in the art at the time the invention was made to synthesize a solid oral composition of valsartan, HCTZ and additives as disclosed by dePadova, Fujimura, Armah, Ku and Dopper and modify the method described by Makino in view of the teachings of Ku (Lachman?) and Tamas. The Examiner also takes this opportunity to contend that Ku's method for the preparation of pharmaceutical compositions containing irbesartan would be successfully applicable to pharmaceutical compositions of valsartan. Applicants respectfully disagree.

In response, Applicants respectfully reiterate the arguments presented above with regard to Muller, Makino, dePadova, Fujimura, Armah, Ku and Dopper. Further, Applicants respectfully submit that Lachman teaches general compression granulation methodology and this general information, in view of the references previously cited, does not teach, motivate or suggest Applicant's processes for forming compressed solid dosage forms of valsartan. In addition, Applicants respectfully submit that even if Tamas does, in fact, teach that powder mixtures can be pressed into tablets under a pressure of 100-120 kN as Examiner suggests, this additional information does not teach, motivate or suggest Applicant's invention in view of the references previously cited.

Applicants also respectfully disagree with the Examiner's belief that Ku's method for the preparation of pharmaceutical compositions containing irbesartan would be successfully applicable to pharmaceutical compositions of valsartan. While both compounds may be angiotensin II receptor antagonists, Ku indicates that irbesartan is a sticky substance, a feature that can cause problems in the tabletting process (Column 1, lines 53-56). In contrast, one of skill in the art understands that valsartan is not a sticky substance, and thus, contrary to Examiner's opinion, it is not *necessarily* true that the method disclosed by Ku to make tablets of irbesartan would also be applicable to make tablets of valsartan. In fact, this is clearly not the case since Ku discloses that the preferred method to make the irbesartan tablets involves a wet granulation process (Column 6, lines 29-31). Thus, there can be no prima facie case of obviousness based on the method disclosed in Ku since the preferred wet granulation process actually teaches away from the unconventional dry tabletting process and the surprising results obtained by Applicants. Thus, the combination of references previously cited by the Examiner in view of Lachman and Tamas cannot render Applicants' invention prima facie obvious. For this reason, and the reasons discussed above, Applicants respectfully request that this rejection be withdrawn.

Applicants believe that the arguments presented above successfully overcome all the Examiner's grounds for rejection and that the claims are allowable.

A Notice of Allowance is respectfully requested.

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If there are any fees due in connection with this communication, including any fees for a required extension of time, such an extension is requested and the Commissioner is authorized to charge the fees to Deposit Account No. 19-0134 in the name of Novartis Corporation.

Respectfully submitted,

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